Neurofibromatosis type 1 (NF1) with an unusually severe phenotype due to digeny for NF1 and ryanodine receptor 1 associated myopathy

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CASE REPORT

Neurofibromatosis type 1 (NF1) with an unusually severe phenotype due to digeny for NF1 and ryanodine receptor 1 associated myopathy

Florence Martin · Veronika Kana · Andrea Capone Mori · Dirk Fischer · Nicolas Parkin · Eugen Boltshauser · Elisabeth Jane Rushing · Andrea Klein

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Abstract We describe a 5-year-old girl with marked hypotonia, poor feeding and reduced facial expression since birth. Congenital myopathy was suspected; muscle biopsy showed unspecific type 1 fibre predominance. The possibility of a ryanodine receptor 1 gene (*RYR1*)-associated myopathy was considered, but not further investigated. At the age of 2 years, she presented with exophthalmos. Brain MRI revealed optic pathway glioma. On clinical examination, she had six café-au-lait spots, thus fulfilling the diagnostic criteria for neurofibromatosis type 1 (NF1). The hypotonia was then attributed to NF1. At the age of 3 years, she developed scoliosis and had an unusually severe motor delay for NF1, as she was not able to walk independently. Dual pathology was suspected, and muscle MRI showed the typical pattern for *RYR1*-related myopathy. This was genetically confirmed with the discovery of two heterozygous mutations. *Conclusion*: NF1 is one of the most frequent genetic diseases in children. *RYR1*-related myopathy is one of the most frequent causes of congenital myopathy. The combination of these two pathologies has not yet been described. In cases of unusual presentations or clinical course, the possibility of genetic "double trouble" should be considered.

Keywords Neurofibromatosis type 1 · Ryanodine receptor 1 · Myopathy · Dual pathology · Central core disease

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F. Martin
Department of Paediatric Neurology, Kantonsspital Winterthur, Winterthur, Switzerland
e-mail: Florence.martin@ksw.ch

V. Kana · E. J. Rushing
Department of Neuropathology, University Hospital Zürich, Zürich, Switzerland

V. Kana
e-mail: Veronika.kana@usz.ch

E. J. Rushing
e-mail: Elisabethjane.rhushing@usz.ch

A. C. Mori
Department of Pediatric Neurology, Kantonsspital Aarau, Aarau, Switzerland
e-mail: andrea.capone@ksa.ch

D. Fischer
Department of Neurology, University Hospital Basel, Basel, Switzerland
e-mail: dirk.fischer@ukbb.ch

D. Fischer
Division of Neuropaediatrics, University Children's Hospital Basel, Basel, Switzerland

N. Parkin
DNA Laboratory, Guy's Hospital, London, UK
e-mail: Nicolas.parkin@gsts.com

E. Boltshauser · A. Klein (✉)
Department of Paediatric Neurology, University Children's Hospital Zürich, 8032 Zürich, Switzerland
e-mail: andrea.klein@kispi.uzh.ch

E. Boltshauser
e-mail: eugen.boltshauser@bluewin.ch

Abbreviation

NF1 Neurofibromatosis type 1
RYR1 Ryanodine receptor 1

Introduction

Neurofibromatosis type 1 (NF1) (OMIM 613113, cytogenetic location on chromosome 17q11.2) is one of the most frequent inherited diseases in childhood with a birth prevalence of 1:3,000. The diagnosis is based on family history and clinical findings [2, 14]. In infancy, hypotonia and developmental delay are often among the first symptoms [7]. Ryanodine receptor 1 gene (RYR1; OMIM 180901, cytogenetic location 19q13.2)-related myopathies are probably the most frequent forms of congenital myopathies with an estimated prevalence of 1:90,000 [8]. Typical central core disease and malignant hyperthermia are usually dominantly inherited, but in recent years, recessively inherited *RYR1*-related myopathies have been increasingly recognised [6]. The typical clinical manifestation in childhood consists of relatively stable proximal, axial and often facial weakness. More generalised weakness and involvement of extraocular muscles have been described in patients with recessive mutations. Orthopaedic complications such as dislocation of the hip, scoliosis and joint laxity are frequent.

The combination of NF1 and *RYR1*-related myopathy has not been described before.

Case report This 5-year-old girl was born at term by caesarean section due to transversal position after an uneventful pregnancy. Her mother and older brother are healthy; the father is affected by ankylosing spondylitis. The girl adapted with an APGAR 1/5/5. Because of respiratory insufficiency and bradycardia, she was resuscitated and ventilated for 2 days. After 5 days, breathing was sufficient, except for rare obstructive apnoeic episodes due to secretion. She had reduced spontaneous movements and facial expression, absent tendon reflexes and reduced muscle tone. Anti-gravity movements were not full. Prader-Willi syndrome, spinal muscular atrophy and myotonic dystrophy were excluded by genetic investigation. Brain magnetic resonance imaging (MRI), creatine kinase, metabolic screening tests, electroencephalography and nerve conduction studies of the tibial nerve were normal. Because of persistent poor feeding at the age of 3 months, a gastrostomy was placed and a muscle biopsy of the quadriceps femoris was performed, which showed variability of fibre size and type 1 fibre predominance and atrophy (Fig 1a, b, c). She was discharged at the age of 4 months. At age of 12 months, she was able to sit independently and started to mouth feed. Cognitive development was mildly delayed. At the age of 21 months, she presented with strabismus, exophthalmos and 6 café-au-lait spots. Brain MRI revealed bilateral

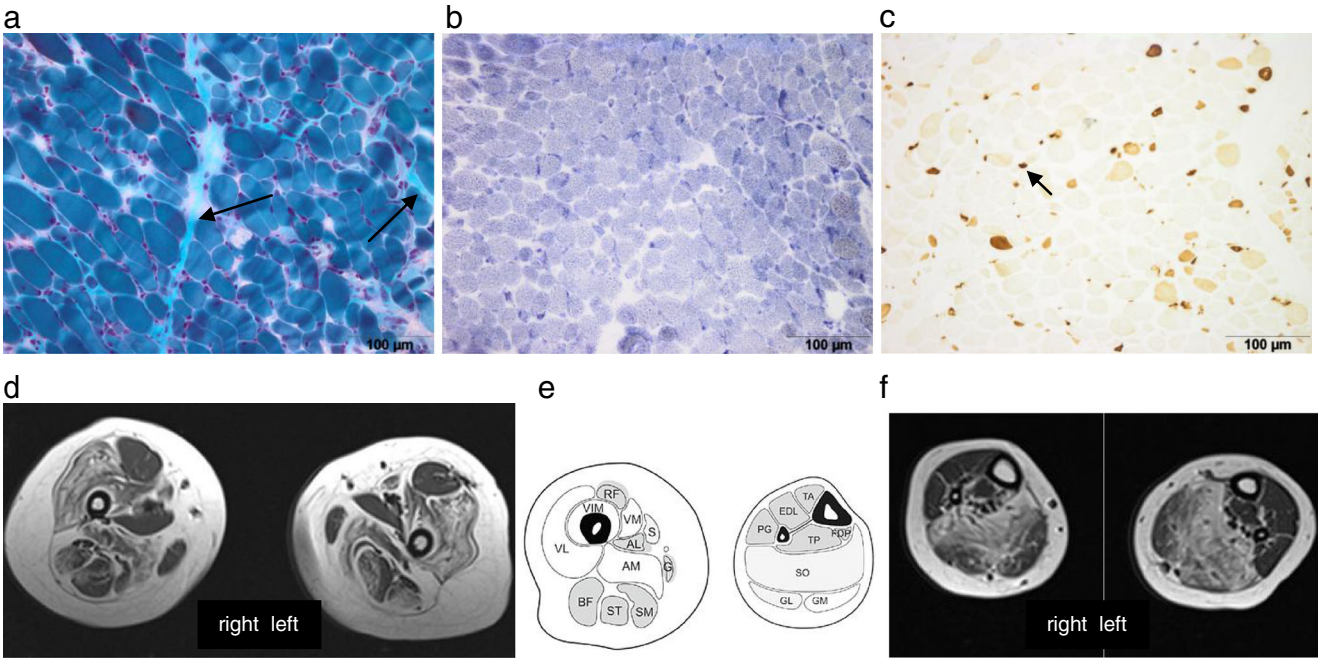

Fig. 1 Biopsy from the quadriceps muscles (**a** Gomori trichrome) showing variation in fibre size, mild endomysial fibrosis (*arrow*) and (**b** NADH) fibre-type uniformity, but no cores and **c** numerous fibres expressing neonatal myosin (*small dark fibres*, see *arrow*). **d** Muscle MRI of the upper leg: selected involvement of adductor magnus (*AD* of schematic image), sartorius (*S*), vastus lateralis (*VL*), vastus intermedius (*VIM*), vastus medialis (*VM*), spared rectus femoris (*RF*), adductor longus (*AD*) and gracilis (*G*). **e** Schematic axial image of left upper and lower leg. **f** Muscle MRI of lower leg: most affected muscle is soleus (*SO*), followed by the lateral head of the gastrocnemius (*GM*)

optic pathway glioma. The diagnostic criteria for NF1 were thus fulfilled. Because of good visual function, the optic pathway glioma was left untreated. The marked motor delay with hypotonia was interpreted as within the limits of a severe NF1 phenotype. She learned to sit up by herself, started to shuffle, but was still not able to stand or crawl. Oral feeding was sufficient to remove gastrostomy. At age of 3 years, she developed freckling as an additional criterion for NF1 and a rapidly progressive thoracic-lumbar scoliosis. Spinal MRI failed to reveal vertebral dysplasia or spinal neurofibroma. The possibility of an additional neuromuscular disorder was re-evaluated. On neurological examination, proximal and facial weaknesses were noted, next to the known hypotonia. Muscle MRI showed symmetrical signal change of vasti, adductor magnus, gastrocnemius and soleus muscles. Rectus femoris, adductor longus, gracilis and the peroneal group muscles were relatively spared (Fig.1d, e). This pattern is suggestive for *RYR1*-related myopathy. Full gene sequencing revealed two novel variants (c.11360-1_11374del16, predicted to remove the splice acceptor site at the start of exon 80; c.14928C>G; p.Phe4976Leu, a point mutation at a position that is highly conserved). Pathogenicity was assessed using bioinformatics software Alamut v2.0. Both unaffected parents carried one mutation (c.11360-1_11374del16 was inherited from the father, c.14928C>G from the mother); therefore, recessive inheritance is suggested.

Discussion

Our case demonstrates the difficulty of discerning hypotonia due to a central problem as in NF1 from weakness caused by a neuromuscular disease in the first few years of life. Even though a myopathy was suspected initially, this differential consideration was rejected at the time when the diagnosis of NF1 was confirmed. The marked motor difficulties and hypotonia were then attributed to a severe NF1 phenotype. Of note, hypotonia, facial dysmorphic features, scoliosis, joint laxity and cognitive impairment have been described in patients with large deletions in the NF1 region [9]. We did not perform genetic testing of NF1 because our patient fulfilled the clinical diagnostic criteria and developed freckling in addition. The differential diagnosis of Legius syndrome (SPRED1; OMIM 611431) was not considered a possibility, because patients with Legius syndrome do not develop optic pathway gliomas [10]. On follow up, the progress in motor development was poor and could not be attributed to hypotonia alone, but was caused by additional proximal weakness. Therefore, the clinical suspicion of an additional underlying congenital myopathy was re-evaluated.

Congenital myopathies are group of neuromuscular diseases with early onset, defined by the predominant histopathological features and structural abnormalities. With recent advances in molecular genetics, it has become clear that different genetic congenital myopathies can share clinical and pathological findings and that many individuals with a genetically confirmed congenital myopathy have only non-specific histopathological features. Cores as the classical histopathological finding of *RYR1*-related myopathies may be absent, and unspecific findings such as fibre-type uniformity or type 1 fibre predominance are frequent, as in our patient. Muscle MRI has been shown to be a helpful tool in the evaluation of congenital myopathies [1, 5]. The typical selective pattern of muscle involvement in *RYR1*-related myopathies led to the genetic investigation in our patient. Two novel mutations were detected; one is a splice site mutation and therefore predicted to be pathogenic. The second variant is a point mutation at a highly conserved position, but the physicochemical difference between the amino acids is low. This mutation has not been reported as a benign polymorphism so far, suggesting a disease causing role in this patient. Since the introduction of diagnostic sequencing of the whole *RYR1* gene, many novel mutations have been detected but assigning pathogenicity is often difficult [6].

The combination of two different genetic diseases has been reported in a few case reports of patients with different neuromuscular disorders, where the combination led to a more severe or unusual phenotype [3, 4, 11–13].

Conclusion

In an unusually severe or atypical presentation, “double trouble” should be suspected. In our patient, careful clinical re-evaluation led to further investigations that ultimately led to the two diagnoses. NF1 is one of the most common genetic diseases in child neurology; the combination with another disorder is therefore a possibility. The diagnosis of the *RYR1*-related myopathy has important implications for genetic counselling and clinical management regarding the risk of malignant hyperthermia for the patient and the family.

Conflict of interest None of the authors declare a conflict of interest.

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